REMARKS

Prior to the present submission, claims 1-23 and 27-34 were pending for examination.

In the present submission, claims 1, 6, 16, 17, 22, and 32 are amended, and claims 4, 5, and 9 are cancelled. Claim 1 has been amended to incorporate the limitations of claim 5; exemplary support for the amendment may be found in originally filed claims 4 and 5. Claim 6 has been amended to incorporate the limitations of claim 9, and exemplary support for the amendment may be found in originally filed claim 9. Claims 16 and 17 are amended in accordance with the Examiner's suggestions, as discussed in more detail below. Exemplary support for the amendment to claims 22 and 23 may be found on page 11, line 25, to page 12, line 20, and in particular page 11, lines 32 to 33, of the application as filed.

The specification is amended to reflect the priority claim and to clarify certain protein sequences recited in the specification in accordance with the Examiner's suggestions, as discussed in more detail below.

No new matter is introduced by these amendments. Notwithstanding the foregoing, Applicants expressly reserve the right to prosecute subject matter no longer or not yet claimed in one or more applications that may claim priority to the present application.

Reconsideration of the claimed invention is respectfully requested in view of the foregoing amendments and the following remarks.

1. Species Election

Applicants acknowledge that the species election requirement has been withdrawn.

2. Specification informalities

The Examiner has requested that the specification be amended to reflect the priority claim under 35 USC 371 of PCT/EP/14542; and that the specification be corrected with regard to a discussion of certain polypeptide sequences which actually refers to the encoding nucleotide sequences. Applicants respectfully submit that the foregoing amendments provide the requested clarification.

3. 35 USC 101

The Examiner has rejected claims 16 and 17 under 35 USC 101 as being drawn to non-statutory subject matter, and has suggested that the claims be amended to refer to "isolated" nucleic acid molecules. Applicants have amended the claims as suggested, and respectfully request that the rejection be withdrawn.

4. 35 USC 112, first paragraph

As an initial matter, Applicants note that claim 1 has been amended to incorporate the limitations of dependent claim 5, which the Examiner has indicated meets the enablement standard. Thus, with regard to claim 1 and those claims which depend therefrom (claims 2, 3, 11, 12, 14, 15, 18-23, and 27-29, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Applicants note that claim 6 has been amended to provide that the mature surfactant protein is selected from the group consisting of surfactant protein B (SP-B) and surfactant protein C (SP-C), and address their comments regarding enablement to claim 6 as amended herein.

Claims 1-4, 6-9, 11, 14, 15, 18-23, and 27-34 have been rejected as failing to meet the enablement standard under 35 USC 112, first paragraph. Applicants respectfully traverse this rejection.

In the office action, it is acknowledged that the specification is enabling with regard to a fusion protein comprising a mammalian SP-B precursor lacking its C-terminal propeptide, or mature SP-B, fused to a plasminogen activator. Applicants submit that one of skill in the art would also acknowledge that the specification is enabling with regard to similar constructs in which SP-B is replaced with SP-C. In this regard, Applicants submit herewith the declaration of Dr. Clemens Ruppert, which addresses the merits of the rejection.

The Office Action takes the position that the claims comprise unspecified variants with regard to the surfactant proteins, and that these variants are not adequately described in the specification. Such a statement is conclusory and is not supported by any evidence of record. With regard to SP-C specifically, Applicants note that this is equally well known to those of skill in the art as is SP-B, which the Office Action acknowledges meets the enablement standard. As

described in some detail in the specification, and in paragraph 5 of the Ruppert declaration, there are four major mammalian surfactant proteins. Of these, SP-A and SP-D are hydrophilic in nature; SP-B and SP-C are both hydrophobic. Each of SP-B and SP-C are synthesized as propeptides by type II alveolar cells, and both are processed to the mature hydrophobic peptide.

It is also noted in the specification that each must be escorted prior to their interaction with surfactant lipids. In the natural environment, the propeptide acts on the molecular level as a "shield" against the highly detrimental function and cell damaging properties of the mature surfactant protein. Thus, the specification teaches page 5 and 6 that a fusion partner (which, again, *in vivo* is the propeptide of the precursor protein) acts as hydrophilic molecular shield that enables the production of the SP-B and SP-C *in vivo* under physiological conditions. Such suitable fusion partners of SP-B or SP-C described in the specification are not only mammalian plasminogen activators but also bacterial proteins such as streptokinase (which is secreted by several species of streptococci) or staphylokinase from staphylococcus aureus (page 9, lines 7-12 and Fig.2).

Dr. Ruppert also notes in paragraph 6 of his declaration that, in a publication subsequent to the filing of the present application, Lukovic *et al., Biochim. Biophys. Acta* 1758: 509-518 (2006) confirms the teachings of the present invention regarding the shared properties of SP-B and SP-C. Lukovic *et al.* report the production and characterization of recombinant forms of human pulmonary protein C (SP-C). The fusion protein of SP-C comprises the hydrophilic nuclease A (SN) of *Staphylococcus aureus* fused to the N-terminus of the mature SP-C (see abstract on page 509 or Fig. 1 on page 510 of Lukovic *et al.*). With respect to the choice of the fusion partner of SP-C, Lukovic *et al.* explain in the results section 3.1 on page 512 that the high hydrophobicity of SP-C was overcome by making a fusion with the hydrophilic nuclease A (SN) from *Staphylococcus aureus* (SN/SP-C, see Materials and methods). This is fully consistent with the teachings of the present invention.

Dr. Ruppert also notes in paragraph 7 of his declaration that the skilled artisan is also aware that SP-B and SP-C share not only structural characteristics as discussed above, but also share functional characteristics, particularly in the context of lung injury and inflammation. For example, Markart *et al., Am. J. Physiol. Lung Cell Mol. Physiol.* 284: L69-L76 (2003), have described alveolar fibrin formation as a histopathological hallmark of the acute respiratory

distress syndrome and of various other acute or chronic lung diseases. They note that under inflammatory conditions, both alveolar macrophages and alveolar epithelial cells may produce and shed significant amounts of procoagulant activity. In a study of the influence of the surfactant proteins on the fibrinolysis-inhibitory capacity of clot-embedded surfactant, they noted that this capacity was further enhanced by the hydrophobic proteins SP-B and SP-C, but reduced by SP-A.

The application as filed explains (for example on page 7, lines 18-20) that the mammalian surfactant protein component of the claimed fusion proteins may preferably be SP-B or SP-C. Page 6, lines 9-12 of the application as filed explains that the fusion proteins of the invention may readily be produced by means of standard recombinant DNA technology such as that described in the molecular cloning textbook of Sambrook *et al.* (cited as reference 28 in the present specification. Thus, it cannot be reasonably argued that one of skill in the art could not *make* the claimed invention. Given the well known similarities in structure and function between SP-B and SP-C, Dr. Ruppert concludes that one of skill in the art could readily extrapolate the working examples involving SP-B to SP-C, and could also *use* the invention as presently claimed. Ruppert declaration, paragraph 8.

The present rejection, which is largely premised on a lack of examples beyond those involving SP-B, is based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that might be encountered in practice. As is often noted in the case law, such an argument does not present a sufficient basis for rejecting a claim under the enablement requirement. See, e.g., *In re Chilowsky*, 229 F.2d 457, 463 (CCPA 1956); *Ex Parte Hicks*, 2000 WL 33673734 at *3. With regard to those sections (*e.g.*, page 7 of the Office Action) which refer to an alleged lack of predictability regarding the hydrophilic surfactant proteins SP-A and SP-D, such remarks are no longer relevant in view of the amended claims.

In conclusion, the claimed invention can be practiced throughout its scope without undue experimentation because the person of ordinary skill with reference to the specification understands its application and need use no more than conventional techniques to apply it. Ajinomoto Co., Inc., v. Archer-Daniels-Midland Co., 228 F.3d 1338; 56 USPQ2d 1332 (Fed. Cir. 2000). No more than routine experimentation would be required to apply the invention

throughout its scope. The enablement standard demands no more. In view of the foregoing, Applicants request that the rejection be reconsidered and withdrawn.

5. 35 USC 112, Secoond paragraph

Applicants respectfully submit that the amendments to claims 22 and 32 render this rejection moot.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and an early notice to that effect is respectfully requested. If the Examiner would like to discuss any remaining issues, Applicants' representative can be reached at (619) 203-3186.

Respectfully submitted,

/Michael A. Whittaker/

Date: December 2, 2010

By:_____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:
Seeger et al.,

Confirmation Number: 4111

Application No.: 10/583,785

Group Art Unit: 1656

Filed: December 18, 2003

Examiner: Chih-Min Kam

Title: NOVEL CHIMERIC PLASMINOGEN ACTIVATORS AND THEIR PHARMACEUTICAL USE

DECLARATION OF DR. CLEMENS RUPPERT

I, Clemens Ruppert, state and declare as follows:

1. I am project leader and deputy lab leader of a basic research lab at the Department of Internal Medicine, Medical Clinic II, Justus-Liebig University of Giessen, Germany , the assignee of the above-referenced '578 application. I am named as co- inventor of the '785 Patent Application. I have been practicing molecular biology techniques, including the expression of mammalian surfactant proteins such as mammalian surfactant protein B (SP-B) and mammalian surfactant protein C (SP-C), for over 15 years. A copy of my *curriculum vitae* is attached to this declaration.

2. I have read and am familiar with the most recent Office Action issued in the '785 Patent Application, which was mailed August 19, 2010. Hereinafter I will refer to this as the "Office Action." I have been informed that the claims have been amended to refer to fusion proteins comprising a mammalian plasminogen activator fused to a mammalian surfactant protein B (SP-B) or surfactant protein C (SP-C).

3. I have been asked to provide comments regarding whether or not a person of ordinary skill in the relevant art, having read the specification, could practice the claimed invention using no more than routine experimentation. I have been informed that this is referred

to as "enablement" of an invention. In this regard, I note that the remarks in the Office Action directed to an alleged lack of enablement of the claimed invention do not comport with the knowledge available to the skilled artisan.

4. The Office Action acknowledges that a fusion protein comprising SP-B and a mammalian plasminogen activator meets the necessary enablement standard. It is clear, however, that the Office Action is unduly focused on the alleged lack of experimental data on the production of a fusion protein of SP-C with a mammalian plasminogen activator. It is my opinion that one of skill in the art would extrapolate the experimental data provided in the patent application for the SP-B fusion protein to a similar construct comprising SP-C.

5. The skilled artisan understands that SP-B and SP-C share certain structural characteristics. There are four major mammalian surfactant proteins. Of these, SP-A and SP-D are hydrophilic in nature; SP-B and SP-C are both hydrophobic. In addition, each of SP-B and SP-C are synthesized as propeptides by type II alveolar cells, and both are processed to the mature hydrophobic peptide. As described in the specification, SP-B and SP-C must each be escorted prior to their interaction with surfactant lipids in order to be properly assembled. In the natural environment, the "propeptide" portion of the SP-B and SP-C precursor acts on the molecular level as the necessary "shield" against the highly detrimental function and cell damaging properties of the mature surfactant protein. Thus, the present specification teaches page 5 and 6 that a fusion partner can also as the necessary shield. Such suitable fusion partners of SP-B or SP-C described in the specification are not only mammalian plasminogen activators but also bacterial proteins such as streptokinase (which is secreted by several species of streptococci) or staphylokinase from staphylococcus aureus (page 9, lines 7-12 and Fig.2).

6. I refer to Lukovic et al, Biochim Biophys Acta. 2006, 1758(4):509-518, which confirms the teachings of the present invention regarding these shared properties of SP-B and SP-C. Lukovic *et al.* report the production and characterization of recombinant forms of human pulmonary protein C (SP-C). The fusion protein of SP-C comprises the hydrophilic nuclease A (SN) of *Staphylococcus aureus* fused to the N-terminus of the mature SP-C (see abstract on page 509 or Fig. 1 on page 510 of Lukovic *et al.*). With respect to the choice of the fusion partner of SP-C, Lukovic *et al.* explain in the results section 3.1 on page 512 that the high hydrophobicity

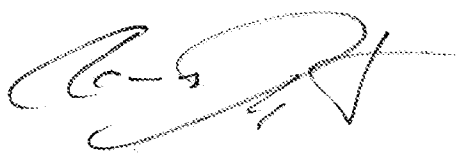
of SP-C was overcome by making a fusion with the hydrophilic nuclease A (SN) from *Staphylococcus aureus* (SN/SP-C, see Materials and methods). This is fully consistent with the teachings of the present specification.

7. The skilled artisan is also aware that SP-B and SP-C share not only structural characteristics as discussed above, but also share functional characteristics, particularly in the context of lung injury and inflammation. For example, Markart et al., Am. J. Physiol. Lung Cell Mol. Physiol. 284: L69-L76 (2003), on which I am named as an author, describes alveolar fibrin formation as a histopathological hallmark of the acute respiratory distress syndrome and of various other acute or chronic lung diseases. The publication further describes that, under inflammatory conditions, both alveolar macrophages and alveolar epithelial cells may produce and shed significant amounts of procoagulant activity. In a study of the influence of the surfactant proteins on the fibrinolysis-inhibitory capacity of clot-embedded surfactant, the publication notes that this capacity was further enhanced by the hydrophobic proteins SP-B and SP-C, but reduced by SP-A.

8. Given the knowledge available in the art and the level of teachings in the present specification, it is my opinion that the claimed fusion proteins may readily be produced by means of standard recombinant DNA technology; and given the well known similarities in structure and function between SP-B and SP-C, it is my opinion that one of skill in the art could readily extrapolate the working examples involving SP-B to SP-C. In view of this, the claimed invention can be practiced throughout its scope with reference to the specification using no more than conventional techniques.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under § 1001 of Capital Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

December 1st, 2010



DR. CLEMENS RUPPERT

Curriculum vitae

Clemens Ruppert, PhD

born 24.04.1969 in Bensheim, Germany, married, three children

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University Education

2001 Dr. rer. nat. (summa cum laude) Saarland University, Saarbrücken, Germany
1995 - 2000 PhD thesis work, Department of Pharmacy and biopharmaceutics, Saarland University; Saarbrücken, German (supervisor: Prof. C.M. Lehr)
1995 Internship Pharmacy at the University Hospital Giessen, Germany
1990 - 1994 Studies of Pharmacy at the Philipps University of Marburg, Germany

Professional Positions

2010 - Project Leader of an individual research project RU907/3-1, funded by the German Research Council (DFG) ("Relative role and interdependence of urokinase and hepatocyte growth factor in mediating epithelial cell-protective effects in lung fibrosis"")
2009 - Project Leader "German Diffuse Parenchymal Lung Disease Network" (BMBF)
2006 - Project leader of the Clinical Research Group "Pathomechanisms and therapy of Lung Fibrosis", funded by the German Research Council
2006 - Faculty member of the Excellence Cluster Cardio-Pulmonary System (ECCPS)
2006 – 2007 Project leader of an individual research project RU907/2-2, funded by the German Research Council (DFG) ("Stellenwert der enzymatisch vermittelten Surfactantkonversion bei respiratorischer Insuffizienz")
2003 - 2006 Research Fellowhip, Collaborative Research Center (Sonderforschungsbereich) SFB 547 "Cardiopulmonary Vascular System" funded by the German Research Council (DFG)
2003 - 2005 Project leader of an individual research project RU907/2-1, funded by the German Research Council (DFG) ("Stellenwert der enzymatisch vermittelten Surfactantkonversion bei respiratorischer Insuffizienz")
2001 - 2003 Postdoctoral Research Fellow, Department of Internal Medicine, Justus-Liebig University Giessen, Germany

Awards and Honours

2000 Travel Award, German Society for Thrombosis and Hemostasis Research (GTH)

Publications

1999 – in total 45 scientific publications, among which are:
36 original, peer reviewed articles exclusively in pubmed listed, native english journals (10 first/senior author), 2 articles in press
3 invited reviews, editorials or commentaries (2 first/senior author),
4 book chapters (4 first/senior author)

Reviewer Responsibilities

Antioxidants and Redox Signaling, American Journal of Respiratory and Critical Care Medicine; American Journal of Respiratory Cell and Molecular Biology; American Journal of Physiology; Atherosclerosis;

European Respiratory Journal; Intensive Care Medicine; Respiratory Research; Thorax; Thrombosis and Haemostasis